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(54) Title: FORMULATIONS FOR TREATMENT OF PAIN COMPRISING VITAMIN B12 AND PHENYLANINE

(54) Titre: FORMULATIONS POUR LE TRAITEMENT DE LA DOULEUR CONTENANT DE LA VITAMINE B12 ET DE LA PHENYLANINE

(57) Abstract

Orally administrable formulations containing a vitamin B¿12 component, preferably hydroxocobalamin, and phenylalanine are described. They may be taken at a specified daily dosage to provide 50 to 5000 mg phenylalanine per day and 0.2 to 50 mg of vitamin B¿12 component. They are used to treat pain or chronic fatigue syndrome. Other drugs or essentiel nutrients may be added such as folic acid, glucosamine or an anti-depressant drug as appropriate.

(57) Abrégé

Cette invention a trait à des formulations administrables par voie orale contenant un composant de la vitamine B¿12, de l'hydroxocobalamine de préférence, et de la phénylalanine. Ces formulations, qui peuvent être prises quotidiennement à des dosages indiqués, de manière à apporter de 50 à 5000 mg de phénylalanine et de 0,2 à 50 mg du composant de la vitamine B¿12 par jour, sont utilisées pour soulager la douleur ou traiter un syndrome de fatigue chronique. Il est possible, si nécessaire, d'ajouter d'autres substances médicamenteuses ou des éléments nutritifs essentiels, tels que l'acide folique et la glucosamine, ou un médicament antidépresseur.

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(30) Priority Data: 9906808.2 24 March 1999 (24.03.99) (71) Applicant (for all designated States except US): KILC LIMITED [GB/GB]; Simcocks, Ridgeway House, R Street, P.O. Box 181, Douglas IM99 1PY, Isle of Mi (72) Inventor; and (75) Inventor/Applicant (for US only): HORROBIN, Davi erick [GB/GB]; Laxdale Limited, Kings Park House, hill Business Park, Polmaise Road, Stirling FK7 9Ji (74) Agent: GALLAFENT & CO.; 9 Staple Inn, London 7QH (GB).	idgewa an (GB id, Fred Laure Q (GB	Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(54) Title: FORMULATIONS FOR TREATMENT OF PA	IN CO	MPRISING VITAMIN B12 AND PHENYLANINE

Orally administrable formulations containing a vitamin B_{12} component, preferably hydroxocobalamin, and phenylalanine are described. They may be taken at a specified daily dosage to provide 50 to 5000 mg phenylalanine per day and 0.2 to 50 mg of vitamin B_{12} component. They are used to treat pain or chronic fatigue syndrome. Other drugs or essentiel nutrients may be added such as folic acid, glucosamine or an anti-depressant drug as appropriate.

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Description

- 1 -

FORMULATIONS FOR TREATMENT OF PAIN COMPRISING VITAMIN B12 AND PHENYLANINE

Pain is a major human problem. It comes in many different forms, such as the pain of an acute injury or surgical

5 procedure, the pain associated with chronic inflammation, for example of the joints, the pain of headaches, including migraine attacks, the pain associated with muscle spasms, and many types of long term, chronic, ill-defined pain. Chronic long-term pain is often associated with nerve

10 damage of one type or another. The nerve damage may result from a medical illness such as diabetes or alcoholism, or from damage to nerves resulting from local physical pressure or injury such as many forms of back pain and lower limb pain, or pain resulting from severance of a

15 nerve with partial regrowth, or pain with no very obvious cause such as fibrositis or fibromyalgia.

Many types of drugs may relieve pain. Currently they fall into six major categories although, as pain mechanisms

20 become better understood, more categories are likely to be discovered. These major categories are the opiates such as morphine, heroin, pethidine, codeine and related compounds; the steroids which work by reducing inflammation; the

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- 2 -

5 non-steroidal anti-inflammatory drugs which inhibit the enzymes cyclo-oxygenase 1, cyclo-oxygenase 2 or both; a group of miscellaneous compounds which sometimes work in the pain associated with nerve damage (neuropathic pain) and whose most important members are the tricyclic 10 antidepressants; anti-migraine agents which often interact with the serotonin system; and a group of compounds which are antagonists of various peptides which are believed to be involved in the production of 15 pain. International publication WO 98/01157 discloses that, in the pain associated with diabetes, the antidepressant lofepramine may be particularly effective, especially when combined 20 with the co-administration of neurotransmitter 15 precursors such as L-phenylalanine and tryptophan and with vitamin B_{12} . Under certain circumstances it was stated that the combination of vitamin B12 with one of 25 the neurotransmitter precursors might be beneficial but there is no disclosure of any particular treatment 20 regimes. 30 We have now surprisingly found that two of the compounds described in the previous application, vitamin B12 and phenylalanine, are unexpectedly effective when presented orally in particular ratios and when the vitamin \boldsymbol{B}_{12} is 35 given in a high absolute dose and in a relatively high ratio to phenylalanine as compared to normal therapeutic doses of vitamin B_{12} . We have also found that this oral 40

doses of vitamin B₁₂. We have also found that this oral combination is effective not just in the pain of diabetic neuropathy but in all forms of chronic neuropathy, in pain associated with the spinal column, including low back pain and sciatica, in pain of unknown origin such as trigeminal neuralgia, and in headaches of many different types, including tension headaches and migraines. In addition to pain we have also found it beneficial in

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chronic fatigue syndromes. Over 80 patients with these various types of pain have been treated with good to

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excellent relief in about three quarters. The relief usually begins within 24 to 72 hours of the first dose, sometimes within 6 hours, and then may show further improvement over one to two weeks. The improvement is then maintained indefinitely. Chronic fatigue usually takes about one week to improve initially and then shows further improvement over several weeks or months. In contrast to all other approaches to relieving pain, administration of formulations according to the present invention does not appear to be associated with any significant adverse effects.

Thus in accordance with a first feature of the present invention there is provided an orally administrable formulation containing a vitamin B₁₂ component and phenylalanine, in a weight ratio of 1/100 to 1/1000, and wherein the concentrations of each are such as to provide, in a daily specified dosage of the formulation, from 50.0 mg to 5000.0 mg phenylalanine and from 0.2 mg to 50.0 mg vitamin B₁₂ component.

The total daily dose of the phenylalanine component may be anything from 50mg to 5000mg, but is preferably from 200mg to 2000mg. The phenylalanine should usually be in 25 the L- or DL-forms. However, recent findings of racemase enzymes in humans which can interconvert D and L amino acids mean that the D-form can also be effective. total daily dose of the vitamin B12 component may be from 0.2mg to 50mg but is preferably from 0.5mg to 5mg. These doses are much higher than oral doses normally used in treating vitamin B_{12} deficiency states. The vitamin B_{12} may be in the form of hydroxocobalamin or cyanocobalamin: however, hydroxocobalamin is the preferred form. This is because hydroxocobalamin is a cyanide antagonist whereas 35 cyanocobalamin is not. Since some forms of nerve damage may be related to cyanide accumulation either because of exposure to toxic cyanide-generating materials or to

- 4 -

5		nutritional deficiency states when cyanide may
		accumulate, or to errors of metabolism which may lead to
		elevated cyanide levels, it is preferable to use
		hydroxocobalamin as the source of vitamin B12.
10	5	Surprisingly, no oral pharmaceutical products containing
		hydroxocobalamin are presently available. All currently
		contain cyanocobalamin. The materials may be formulated
		together in any appropriate dosage form known to those
15		skilled in the art. Appropriate dosage forms include
	10	tablets, hard or soft gelatin capsules, powders,
		micro-encapsulated products, solutions, syrups,
		emulsions, mousses, gels, or other oral forms known to
20		those skilled in the art. The daily dose may be taken at
		one time, or divided, for example into two, three or four
	15	portions.
25		The formulations may also contain other drugs or
25		The formulations may also contain other drugs or nutrients provided that the ratios of vitamin B_{12}
25		nutrients provided that the ratios of vitamin B_{12}
25	20	nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of
25	20	nutrients provided that the ratios of vitamin B_{12}
	20	nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed.
	20	nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the
	20	nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis.
	20	nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve
30		nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve the pain whereas the glucosamine helps to provide long
30		nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve
30		nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve the pain whereas the glucosamine helps to provide long term repair of the damaged joints. Folic acid is another ingredient of particular value since it acts
30		nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve the pain whereas the glucosamine helps to provide long term repair of the damaged joints. Folic acid is another ingredient of particular value since it acts synergistically with vitamin B_{12} in several metabolic
30		nutrients provided that the ratios of vitamin B_{12} component to phenylalanine, and the total doses of vitamin B_{12} component and phenylalanine are as claimed. An additional ingredient of particular value is glucosamine or glucosamine derivatives when the formulation is used to relieve the pain of arthritis. The vitamin B_{12} and phenylalanine act rapidly to relieve the pain whereas the glucosamine helps to provide long term repair of the damaged joints. Folic acid is another ingredient of particular value since it acts

35 EXAMPLES

1. Tablets containing 200mg L-phenylalanine with

added to the formulation in an appropriate dose.

antidepressant drug of any appropriate type may also be

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5		between 2mg and 0.2mg of vitamin B_{12} , either as
		cyanocobalamin or hydroxocobalamin.
10	_	2. Tablets as in 1 but containing 500mg or 1000mg of
10	5	L-phenylalanine in a ratio to the vitamin B_{12} component of 1/100 to 1/1000.
		3-4. Formulations as in 1 and 2 but using hard or soft
15	10	gelatin capsules
		5. A syrup containing 500mg L-phenylalanine and between
20		5 and 0.5mg of vitamin B_{12} component in 10ml, together with appropriate flavouring.
	15	6-10. Formulations as in 1-4 but in which the
25		L-phenylalanine is replaced by DL-phenyalanine or D-phenylalanine.
		11-15. Formulations as in 1-4 in which in addition there
	20	is included 100-500mg of glucosamine in an appropriate
30		form as an anti-arthritic agent.
		16-20. Formulations as in 1-4 in which other essential
	25	nutrients are included, particularly folic acid in a 1:1
35	23	ratio with vitamin B ₁₂ .
		21-24. Formulations as in 1-4 in which an antidepressant
		drug of any type is added in an appropriate dose.
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Claims

- 6 -CLAIMS

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An orally administrable formulation containing a vitamin B₁₂ component and phenylalanine, in a weight ratio of 1/100 to 1/1000, and wherein the concentrations of each are such as to provide, in a daily specified dosage of the formulation, from 50.0 mg to 5000.0 mg phenylalanine and from 0.2 mg to 50.0 mg vitamin B₁₂ component

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2. A formulation according to Claim 1 wherein the vitamin B_{12} component is hydroxocobalamin.

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- 3. A formulation according to Claim 1 wherein the 15 phenylalanine is L-phenylalanine.
 - 4. A formulation according to Claims 1, 2 or 3 wherein the phenylalanine is DL-phenylalanine, or D-phenylalanine.

- 5. A formulation according to any one of Claims 1 to 4 wherein the daily specified dosage of the formulation contains 200.0 mg to 2000.0 mg phenylalanine.
- 25 6. A formulation according to any one of Claims 1 to 5 wherein the daily specified dosage of the formulation contains 0.5 mg to 5.0 mg of the vitamin B_{12} component.
- A formulation according to any one of the preceding
 Claims and additionally containing one or more essential nutrients or drugs.
- A formulation according to any one of the preceding Claims and additionally containing glucosamine or one or
 more glucosamine derivatives.
 - 9. A formulation according to any one of the preceding

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5		Claims and additionally containing folic acid or related bioactive derivative.
10	5	10. A formulation according to any one of the preceding Claims and additionally containing an anti-depressant drug.
	10	11. A method of treatment of pain or chronic fatigue syndrome which comprises the oral administration of a formulation in accordance of any one of the preceding Claims.
20	15	12. A method according to Claim 11 wherein the pain is diabetic pain due to peripheral nerve damage.
25		13. A method according to Claim II wherein the pain is a chest, abdominal, limb, pelvic, back or other pain originating from the spinal column.
30	20	14. A method according to Claim 11 wherein the pain is a headache or migraine headache.
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INTERNATIONAL SEARCH REPORT

tra Aonal Application No PCT/GB 00/01092

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